constitutes new matter, i.e.:

> The added material which is not supported by the original disclosure is as follows: "SEQ. ID. NO.: 339737 Gen Bank Accession No. M10988".

The Office action is incorrect, in that the "added material" allegedly "not supported in the original disclosure" is, in fact, found in the specification as originally filed, at page 15, lines 26-27, which reads (*emphasis added*):

> The DNA sequence is available from *Gen Bank under accession no. M10988, SEQ ID NO:339737.*

The added material, thus, being supported in the original disclosure, i.e., it does not constitute new matter, withdrawal of the objection is in order.

According to the Office action, the rejection of record under 35 USC 103(a), based on the combined teachings of Mouritsen and Eisner with Pennica *et al.,* Shirai *et al.,* or Wang *et al*, further in view of Jones, and/or further in view of Pannina-Bordigon, was maintained, as applied against claims 50-76. Reconsideration of the rejection is requested.

Applicants incorporate herein by reference their remarks addressing the aforesaid rejection under §103(a) as contained in their Amendment filed July 20, 2000.

Furthermore, Applicants submit that the justification of the §103(a) rejection found in the statement of rejection selects only those sequences from Jones that fit with the presently claimed invention, without there being any motivation in the prior art to do so. Thus, the rejection uses the presently claimed invention as a blueprint for picking from among the many sequences disclosed in the reference. This amounts to improper hindsight analysis and reconstruction, which cannot be the basis for a rejection under 35 USC 103(a). "One cannot use hindsight reconstruction to pick

and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciate of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). It is the combined teachings of the prior art, taken as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ 2d 1053 (Fed. Cir. 1991).

It must be recalled that Jones is a review of numerous partly conflicting observations reported by a number of authors up to 1992. Attention is directed to those analogues disclosed in the instant application that did not work (i.e., 2-1, 2-4, 30-1 and 30-4). Applicants provide the following comparison between the non-working analogues, on the one hand, with Jones' observations, on the other, taken in conjunction with a fair reading of Mouritsen.

First, based on the murine data disclosed in Mouritsen, one skilled in the art would have considered that any substitution would work (see example 3 for details). In example 3 it was shown that all 3 substitutions in the wild-type murine TNFα. However, it was not clear from this example whether this would lead to a down regulation of the TNFα by clearance, e.g., because the TNFα-antibody complex was eaten by macrophages or by neutralization, as is the case in the present application. According to the reference:

- MR 103 was substituted in position 26-35;
- MR 105 was substituted in position 5-20; and
- MR 106 was substituted in position 126-140.

Thus (the substitution in) MR 105 incorporates the whole of the "forbidden" B strand in the back β-sheet (see Jones, Figure 4) and most of the 2-1 and 30-1 sequence.

MR 103 partially overlaps the 30-1 sequence and is, in fact, a substitution in the connecting loop between the B and B^1 strands, which is to be avoided (specification, page 21).

So, based on Mouritsen, alone, there would have been no motivation for one skilled in the art to avoid the B-strand and connection loops in the back β-sheet.

Mutation in the 26-35 region was known to detoxify TNF_α, as taught in van Ostade (submitted herewith). Van Ostade was published after Jones; so, both from a detoxification point of view, and from the point of view concerning the ability to raise antibodies in mice, a person skilled in the art would, certainly, have considered that substitution in the B strand and B-B1 connecting loop would work.

The statement of rejection (Office Action, page 6, line 6) alleges that putative receptor binding sites would have been obvious targets for substitution. Assuming, arguendo, this allegation to be correct, substitution at 11-14 (which encompasses the N-terminal of the B strand) would have been just as obvious a choice as substitution at 49 to 57.

Also, the statement of rejection (Office Action, page 7) relies on Fig. 13, focusing on mutations that abrogate biological activity, to support the conclusion of obviousness. Assuming, arguendo, the statement of rejection to be correct in this respect, then Pro 117 and Tyr 119 (see also table 3) would have, also, been obvious likely candidates. However, both Pro 117 and Tyr 119 are in the G strand, which does not work.

Summing up, although Mouritsen must be regarded as the closest prior art, it gives no hint as regards the criticality of the proper sites for substitution and Jones provides no further help since

there is not enabling teaching in Jones as regards which parts of the molecule would be proper targets for substitution irrespective of which overall target criterion was selected. Jones reports likely targets both within those strands of the molecule (B&G strand in the back β-sheet) where the applicants' data have proven that neutralizing antibodies are not formed and identified those parts where neutralizing antibodies are formed.

In addition to the foregoing, patentability is further demonstrated by the surprising and unexpected results obtained in accordance with the invention presently claimed. In this respect, attention is direct to the present specification, page 18, lines 17-32, i.e.:

> A person skilled in the art who wanted to construct a detoxified and yet immunogenic TNFα molecule according to WO 95/05849 would therefore as the first choice insert the immunodominant T cell epitope in the back β-sheet of the TNFα monomer. Modifications of this area would thus most probably interrupt the biological activity of TNFα and leave the receptor-accessible front β-sheet free for interaction with antibodies. This is also consistent with the discussion of the site-directed mutagenesis in the tightly packed core of the β-sandwich discussed above.
>
> However, surprisingly[,] it is not so. As it will appear from the test results below, the result was quite the contrary, since substitutions comprising the B and G strands of the back β-sheet surprisingly provided TNFα analogs which were unable to induce neutralizing antibodies against TNFα. On this background the modified human TNFα molecules according to the present invention are characterized in that the substitution has been made in regions of the TNFα molecule which do not comprise the B and G strands of the back β-sheet of the molecule.

Thus, any *prima facie* case of obviousness is effectively rebutted by the surprising and unexpected results obtained in accordance with the presently claimed invention, as reported in the in the present specification.

Favorable action is requested.

Respectfully submitted,

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